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Predictors of fractures in patients with stage VD chronic kidney disease treated with hemodialysis

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Bone pathology begins in the early stages of chronic kidney disease (CKD), but clinical consequences — bone pain and fractures — occur mainly at stage 5 of the disease (VD) in patients who use methods renal replacement therapy. Objective. To find out the frequency, localization and possible predictors of fractures in patients with CKD VD stage on the background of hemodialysis according to the results of a prospective study. Methods. 254 patients were included in the cohort prospective open study with CKD VD stage, which was treated with hemodialysis hemodialysis during 2018–2022. The study was conducted in two stages. On the first, based on the analysis of medical documentation, received data on the presence of fractures of all localizations, diabetes, hypertension, secondary hyperparathyroidism, hyperhydration, type of initial vascular access, eKt/V, body mass index (IMT), peripheral vascular disease. At the second stage, a prospective study of new cases of fractures was conducted. Results. Examined72 (32.3 %) women and 151 (67.7 %) men, average age — (49.4 ± 14.03) years — did not differ significantly depending on gender (p = 0.1088). The most frequent cause of CKD stage VD was glomerulonephritis — 111 patients (49.77 %). At the time of the beginning of observation, 30 cases were ascertained fractures in 26 patients, and at the end — 62 in 51 patients. By the results of univariate Cox regression analysis it was established that independent predictors of occurrence new fractures are the patient's age, female gender, smoking, presence of peripheral vascular diseases, BMI, as well as serum albumin, parathyroid hormone, calcium, phosphorus, alkaline phosphatase, and vitamin D levels. Conclusions. The developed method of fracture risk assessment for patients with CKD VD stage on the background of hemodialysis is individualized, accessible in execution and interpretation, allows to distinguish patients with increased risk the occurrence of fractures with the help of standard bases clinical and laboratory indicators.

Патологія кісток починається на ранніх стадіях хронічної хвороби нирок (ХХН), але клінічні наслідки — біль у кістках і переломи — виникають переважно на 5-й стадії захворювання (УД) в пацієнтів, яким застосовують методи нирково-замісної терапії. Мета. З'ясувати частоту, локалізацію та можливі предиктори переломів у хворих на ХХН УД стадії на фоні гемодіалізу за результатами проспективного дослідження. Методи. До когортного проспективного відкритого дослідження включено 254 пацієнти із ХХН УД стадії, яким застосовано гемодіаліз протягом 2018–2022 рр. Дослідження проведено в два етапи. На першому на підставі аналізу медичної документації отримано дані щодо наявності переломів усіх локалізацій, цукрового діабету, артеріальної гіпертензії, вторинного гіперпаратиреозу, гіпергідратації, типу ініціального судинного доступу, eKt/V, індексу маси тіла (ІМТ), захворювання периферичних судин. На другому етапі проведено проспективне вивчення нових випадків переломів. Результати. Обстежено 72 (32,3 %) жінок і 151 (67,7 %) чоловік, середній вік — (49,4 ± 14,03) років — значуще не відрізнявся залежно від статі (p = 0,1088). Найчастішою причиною ХХН УД стадії був гломерулонефрит — 111 пацієнтів (49,77 %). На момент початку спостереження констатовано 30 випадків переломів у 26 пацієнтів, а на прикінці — 62 у 51 хворого. За результатами уніваріабельного регресійного аналізу Кокса встановлено, що незалежними предикторами виникнення нових переломів є вік пацієнта, жіноча стать, тютюнопаління, наявність захворювань периферичних судин, ІМТ, а також рівні в сироватці крові альбуміну, паратгормону, кальцію, фосфору, лужної фосфатази та вітаміну D. Висновки. Опрацьований метод оцінювання ризику переломів для пацієнтів із ХХН УД стадії на фоні гемодіалізу є індивідуалізованим, доступним у виконанні й інтерпретації, дозволяє виділити пацієнтів із підвищеним ризиком виникнення переломів за допомогою стандартних базових клінічних і лабораторних показників. Ключові слова. Предиктори переломів, нирки, гемодіаліз, лабароторні показники.

Key words. Predictors of fractures, kidneys, hemodialysis, laboratory parameters

Introduction

Bone abnormalities are observed in the early stages of chronic kidney disease (CKD), but clinical consequences, such as bone pain and fractures, occur mainly in the 5th stage of the disease secondary to administration of renal replacement therapy (RRT). Disorders of mineral and bone metabolism in patients with CKD (osteoporosis, hyperphosphatemia, hypocalcemia, followed by the development of hypercalcemia, reduced level and activation of vitamin D, secondary hyperparathyroidism, increased fibroblast growth factor-23) and the impact of drugs probably increase the risk of fractures [1]. To date, it has been proven that the risk of fractures in CKD patients who undergo RRT is higher than in the general population; and in those receiving hemodialysis, it is higher than in patients with peritoneal dialysis or kidney transplantation [2]. Markers of mineral and bone metabolism in patients with CKD improve significantly after successful kidney transplantation, but can be related to additional risks of fractures due to steroid-induced osteoporosis [1]. The frequency of fractures in patients with VD stage of CKD is associated with high rates of morbidity, mortality and poor quality of life in patients receiving hemodialysis. The risk of death increases by 3.7 times, hospitalizations by 4 times [3]. In addition, fractures are a serious economic burden, so it is important to determine independent predictors of their occurrence in patients undergoing RRT.

The true risk and predictors of fractures in patients with stage 5 CKD who receive hemodialysis and their relationship with markers of mineral and bone metabolism in patients with CKD have been little studied, and the results of large-scale, including nationwide, studies of fractures in patients, undergoing hemodialysis, peritoneal dialysis and kidney transplantation are contradictory [4].

Purpose: on the basis of a prospective study, to establish the frequency, localization and possible predictors of the occurrence of fractures in patients with VD stage of CKD, treated with the help of hemodialysis.

Material and methods

The cohort prospective open study included 254 patients with VD stage of CKD who underwent hemodialysis during 2018–2022 at Kyiv City Scientific and Practical Center of Nephrology, which is the clinical base of the Department of Efferent Technologies of the State Establishment «Institute of Nephrology of the National Academy of Sciences of Ukraine»; Department of Hemodialysis and Orthopedic and Traumatological Center of the Communal Non-Profit Enterprise of Kyiv Regional Council «Kyiv Regional Clinical Hospital», which is the base of P. L. Shupyk National University of Health Care of Ukraine, Department of Orthopedics and Traumatology No. 2.

The average duration of hemodialysis at the time of inclusion in the study was (40.34 ± 5.17) months, the cumulative duration of treatment was 537.8 per 100 patient-years (p/y).

Among the people who participated in the study, 223 signed the informed consent. The research protocol was approved by the local Ethics Committee of Kyiv Regional Clinical Hospital. The criteria for inclusion in the study were: age over 18 years, hemodialysis, permanent vascular access — arteriovenous fistula (AVF), ability to adequately cooperate in the research process. Exclusion criteria: age under 18 years, eKt/V less than 1.2 per hemodialysis session and/or duration of hemodialysis less than 12 h/week, history of kidney transplantation, hospitalization for any reason, and/or signs of infection within a month before the study, fever, comorbidities in the acute phase, mental disorders, inability to adequately cooperate during the study. We used clinical data, medical documentation (including the operation protocol), and orthopedists' reports to identify the events of the fracture and determine its localization (femur, pelvis, bones of the upper or lower limb, vertebrae, ribs, sternum, skull). Several anatomically distant fracture sites in one patient were registered as separate cases.

Stages of the study

The study was conducted in two stages. The first stage involved assessment of the medical documentation of dialysis patients to obtain data on fractures of all localizations, diabetes, hypertension, secondary hyperparathyroidism, hyperhydration, type of initial vascular access, eKt/V, body mass index (BMI), peripheral vascular disease.

In addition, all patients included in the study underwent a routine laboratory examination to determine the serum levels of hemoglobin, albumin, phosphorus, calcium, parathyroid hormone (PTH), vitamin D, alkaline phosphatase, ferritin, and C-reactive protein (CRP).

At the second stage of the investigation, a prospective study of new cases of fractures was performed. The primary endpoint was the incidence of new fractures. Prospective follow-up of patients was carried out from the moment of inclusion in the study until death, loss of contact with him or the end of the study on 1 December 2022. Its average duration was (35.5 ± 17.8) months. The cumulative period of prospective observation was 553.6 p/y.

Determination of risk factors

Covariates identified as potential risk factors for fractures were age, sex, BMI, cause of kidney disease (diabetes mellitus or non-diabetogenic kidney damage), concomitant diseases (peripheral vascular disease, secondary hyperparathyroidism, smoking, type of initial vascular access for hemodialysis (AVF or subclavian catheter), biochemical parameters (serum albumin, serum phosphorus, calcium level, alkaline phosphatase activity, intact PTH, vitamin D, CRP). Laboratory examination of patients was performed monthly, fasting before a hemodialysis session. Biochemical parameters used as potential predictors of occurrence of fractures, given as the average values of the values determined in the last 3 months before the patient's inclusion in the study.

Statistical processing of the obtained results was carried out on a personal computer using the MedCalc software, Ostend, Belgium (version 19.3, individual license with permanent update) taking into account the verification of indicators for normal distribution. Under these conditions, the results are presented as mean values of indicators (M) and mean square deviation (SD); median (Me) and interquartile range [Q25; Q75] in the case of a distribution that differs from normal. Indicators of qualitative characteristics are given in the form of absolute and relative frequencies. The probability of differences was assessed by the Student's test (under normal distribution conditions), the non-parametric Mann-Whitney U-test (under normal distribution), and the χ^2 test. The difference in frequencies in groups of paired observations was compared using McNemar's χ^2 test. All tests were two-sided; for all types of analysis, differences were considered statistically significant at $p < 0.05$. Univariate and multivariate Cox regression statistical analysis was used to establish the predictive properties of the studied demographic, clinical, and laboratory parameters determined at the beginning of the observation, based on the results of which the hazard ratio (HR) of the primary endpoint was determined. Statistically significant factors obtained by univariate analysis were used as variables in a multivariable Cox proportional hazards model. Factors that remained significant in multivariate analysis were interpreted as independent predictors of new fractures in patients with CKD VD stage undergoing hemodialysis. Testing of null hypotheses was carried out at the significance level of $p \leq 0.05$ [5].

Results and their discussion

Among the examined cohort, there were 72 (32.3 %) women, 151 (67.7%) men, the average age was (49.4 ± 14.03) years and did not differ statistically significantly depending on gender: women — (51.77 ± 15.67) years old, men (48.46 ± 13.69), $p = 0.109$. The most frequent cause of CKD stage VD was glomerulonephritis — 111 patients (49.77 %).

The main clinical and laboratory parameters of the patients are presented in Table 1.

The frequency of fractures in the studied cohort of patients is given in Table 2. In general, it should be noted that at the time of the beginning of the observation, 30 cases of fractures in 26 people were ascertained. At the end of the study, 51 patients had 62 fractures.

Thus, by the time the study was completed, an increase in the specific gravity of hemodialysis patients with fractures was almost doubled (by 96 %), and the number of fracture cases increased by 106 %. It stands to mention that 9 patients had 2 or more fractures, 2 had fractures in three anatomical areas. Both at the beginning and at the end of the study, femur fractures were the most common. Th e share

Table 1

General characteristics of the studied cohort (n = 223)

Indicator	Value
Diabetes mellitus, (n / %)	53 / 23.80
Diseases of peripheral vessels, (n / %)	45 / 20.20
Duration of hemodialysis at the beginning of the study, (months)	40.34 ± 5.17
Smoking, (n / %)	54 / 24.20
eKt/V (M ± SD)	1.38 ± 0.15
BMI, (kg/m²; M ± SD)	24.10 ± 3.90
Type of vascular access at the beginning of hemodialysis, (AVF, n / %)	137 / 61.43
Ejection fraction L_V, (%, M ± SD)	54.36 ± 8.80
Hyperhydration, (n / %)	12 / 5.40
Arterial hypertension, (n / %)	194 / 86.90
Secondary hyperparathyroidism, (n/%)	174 / 78.00
Laboratory indicators, M ± SD or Me [Q25; Q75]	
Albumin, (g/l)	34.30 ± 5.00
Hemoglobin, (g/l)	88.10 ± 14.80
Hematocrit, (%)	29.70
CRP, (mg/l)	6.10 ± 1.60
Ferritin, (ng/ml)	405 [284; 728]
Phosphorus, (mmol/l)	1.90 ± 0.41
Calcium, (mmol/l)	2.29 ± 0.18
Parathyroid hormone, pg/ml	465.20 [403.00; 537.90]
Alkaline phosphatase, unit/l	168.00 ± 34.71
Vitamin D	32.66 ± 9.20

of patients with them doubled during the period of prospective observation (p = 0.026). Statistically significant differences were also established as a result of the analysis of the increase in cases of other fractures (8.52 % vs. 3.59 %, p = 0.029). At the same time, no significant increase in fractures of the humerus, tibia and forearm was found during the period of prospective observation, statistically significant p = 0.356; p = 0.479; p = 0.312, respectively.

The rate of primary incidence of fractures in the studied cohort was 5.8 per 100 p/y. The specified indicator was significant only for femur fractures and other fractures, and was 2.35 and 1.99 per 100 p/y, respectively.

Primary endpoints were achieved by 25 (11.22 %) patients within 553.6 p/y. In order to determine the predictors of new cases of bone fractures using Cox regression analysis, the demographic, clinical and laboratory characteristics of the patients at the time of inclusion in the study were analyzed (Table 3).

Univariable Cox regression analysis showed that independent predictors of the occurrence of new fractures were patient age, female gender, smoking, peripheral vascular disease, BMI, as well as serum levels of albumin, parathyroid hormone, calcium, phosphorus, alkaline phosphatase, and vitamin D (Fig. 1).

During further analysis, statistically significant factors were analyzed using a multivariate Cox regression model. High prognostic values of HR (hazard ratio) were determined for the following independent predictors of fracture risk in patients with CKD VD stage receiving hemodialysis: age, serum albumin, alkaline phosphatase, and vitamin D (χ^2 model = 57.389, ss = 4, p < 0.0001) (Table 4).

Table 2

The structure and frequency of fractures in patients with VD stage of CKD receiving hemodialysis (n = 223)

Fracture, bone	At the beginning of the study (n / %)	At the end of the study (n / %)	Morbidity rate (per 100 p/y)	p
Femoral (including neck, transtrochanteric fracture)	12 / 5.38	25 / 11.21	2.35	0.0002
Bones of the lower leg	4 / 1.79	7 / 3.14	0.54	0.2500
Humerus	3 / 1.35	5 / 2.24	0.36	0.5000
Bones of the forearm	3 / 1.35	6 / 2.70	0.54	0.2500
Others (pelvis, ribs, vertebrae, clavicle, sternum, hand)	8 / 3.59	19 / 8.52	1.99	0.0010
In total, patients with fractures	26 / 11.66	51 / 22.87	—	0.0018

Table 3

Results of univariate Cox regression analysis for risk assessment of primary endpoint of the study

Indicator	HR	95 % DI	p
Age, years	1.1214	1.0638 – 1.1587	0.0450
Gender (female vs. male)	2.9057	1.3168 – 6.4118	0.0083
Smoking (yes vs no)	2.5247	1.1313 – 5.6345	0.0238
Albumin, g/l	0.8207	0.8167 – 0.9513	0.0088
Hemoglobin, g/l	1.0015	0.9747 – 1.0289	0.9159
Phosphorus, mmol/l	2.3700	1.0798 – 5.2017	0.0314
Parathyroid hormone, pg/ml	1.0041	1.0026 – 1.0056	< 0.0001
Calcium, mmol/l	0.1412	0.1200 – 0.1949	0.0067
Alkaline phosphatase	1.0105	1.0065 – 1.0145	< 0.0001
Vitamin D, ng/ml	0.9358	0.9075 – 0.9651	< 0.0001
CRP, mg/l	0.9140	0.7150 – 1.1685	0.4745
BMI, kg/m²	0.8671	0.7634 – 0.9850	0.0283
DM (yes vs no)	0.8916	0.3335 – 2.3837	0.8171
Diseases of peripheral vessels	3.0031	1.3383 – 6.7390	0.0077
Type of vascular access (CVC vs AVF)	0.5074	0.2019 – 1.2755	0.5074

Note. CVC — central venous catheter

Next, ROC curves were constructed, reflecting the relationship between the development of new cases of fractures and continuous numerical variables included in the model for predicting new cases of fractures (Fig. 2).

Critical levels of serum albumin (≤ 31.4 g/l; AUC = 0.763; 95 % CI: 0.663–0.784; sensitivity 72.00 %; 95 % CI: 50.6–87.9; specificity 71.72 %; 95 % CI: 64.9–77.9; p < 0.0001), alkaline phosphatase (more than 197.7 units/l; AUC = 0.840; 95 % CI : 0.785–0.885; sensitivity 88.00 %; 95 % CI: 68.8–97.5; specificity 78.79 %; 95 % CI: 72.4–84.3; p < .0001), vitamin D (≤ 23.5 mmol/L, AUC = 0.815, 95 % CI: 0.758–0.864, sensitivity 92.00 %, 95 % CI: 73.0–99.0, specificity 73.23 %, 95 % CI: 66, 5–79.3; p < .0001) and age of patients (over 49 years; AUC = 0.633; 95 % CI: 0.566–0.697; sensitivity 76.00 %; 95 % CI: 54.9–90.6; specificity 53.03 %; 95 % CI: 45.8–60.1; p = 0.0172).

Table 4

Results of multivariate Cox regression analysis to assess predictors of achieving the primary endpoint of the study

Indicator	B	HR	95 % DI	P
Age, years	0.039180	1.0400	1.0117–1.0690	0.0053
Albumin, g/l	–0.136900	0.8720	0.7926–0.9594	0.0049
Vitamin D, ng/ml	–0.068390	0.9339	0.8981–0.9711	0.0006
Alkaline phosphatase	0.007829	1.0079	1.0038–1.0119	0.0001

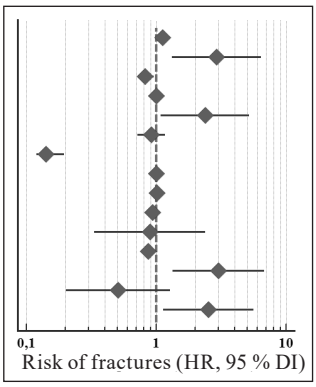

Fig. 1. Risk factors for new cases of fractures in patients with VD stage of CKD receiving hemodialysis

Therefore, taking into account the results of the ROC analysis, our data showed that the independent predictors of the risk of bone fractures in patients with CKD VD stage undergoing hemodialysis are: age over 49 years, serum albumin at the level of 31.4 g/ l or less, alkaline phosphatase more than 197.7 units/l, vitamin D at the level of 23.5 ng/ml or less.

According to the results of individual analysis, taking into account the clinical significance of markers of mineral and bone metabolism in patients with CKD, it was established that the level of PTH in the blood serum exceeded the reference values (over 585 pg/ml) in 20 (80.0 %) and 119 (60.1 %) patients in whom episodes of fractures were recorded or not during the prospective observation, respectively (p = 0.0535). In addition, a significantly higher content of phosphorus in blood serum ((2.04 ± 0.34) mmol/l vs. (1.84 ± 0.28) mmol/l, p = 0.005) was found in people with fractures than without them against the background of a PTH indicator of more than 585 pg/ml.

Discussion

Large-scale, including nationwide, studies are being conducted around the world to determine the risk of fractures in patients with CKD treated with hemodialysis, peritoneal dialysis, and kidney transplantation. We received results from two dialysis centers and the orthopedic and trauma center of Kyiv Regional Hospital. All radiologically confirmed fractures in patients who received hemodialysis in city and regional dialysis centers during the specified period were analyzed. Our data coincided with the data

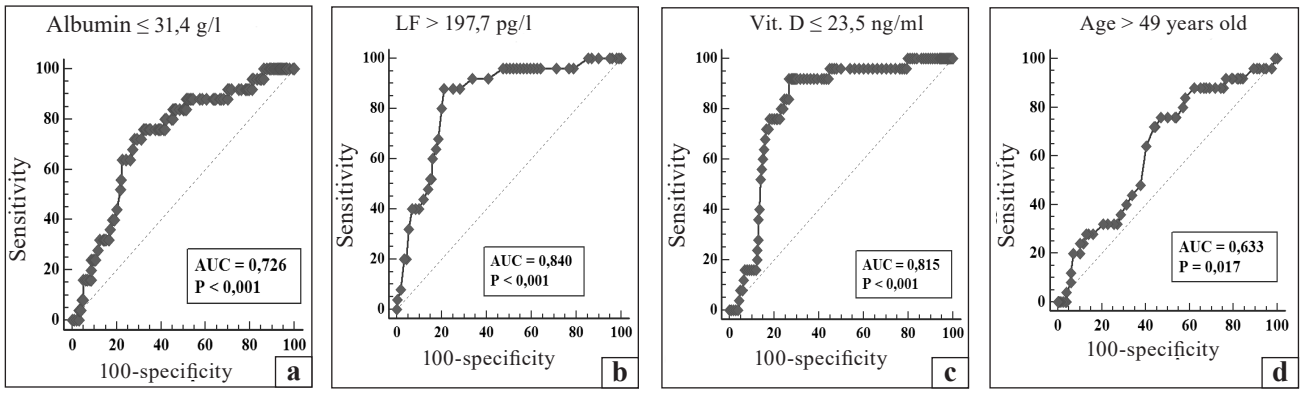

Fig. 2. ROC-curves of the use of serum parameters for the prediction of new cases of fractures in patients with VD stage of CKD undergoing hemodialysis: a) albumin; b) alkaline phosphatase; c) vitamin D; d) age

submitted by Korean authors in 2022, who proved the relationship of hemodialysis with the highest risk of fractures (57.4 per 1000 p/y) [2]. On the basis of a retrospective analysis of patients from all specialized hospitals in the west of Scotland on 7 July 2010, the relative risk of fractures in hemodialysis patients was determined to be 99.2 per 1000 p/y, which is ~2.5 times higher than in people after kidney transplantation. In addition, it was established that fractures of the radius, foot, and femur were the 3 most common localizations (n = 53; 47; 46, respectively) [1]. We, like other researchers [2–4], determined the largest number of femur fractures compared to others. This may be due to patients' susceptibility to falls, given their comorbidities and associated complications (e. g., diabetic neuropathy), causing autonomic dysfunction and loss of sensory or motor function [6, 7]. Unlike the Scottish researchers [1], we found infrequent fractures of the radius and foot. In addition, compared to fractures of the hip and other long bones, clinical vertebral fractures were infrequent (3.1 % of our cohort of patients), and 55.3 % among 387 patients were indicated in [8]. The authors determined a high prevalence of all, including past, vertebral fractures in patients treated with hemodialysis, regardless of symptoms, as identified radiologically using specialized software for quantitative vertebral morphology (MorphoXPress). We studied the frequency of symptomatic fractures only. Increasing age was independently associated with an increased risk of fractures, which is consistent with most studies [6, 9–10], as well as female gender [1, 2, 4]. Contrary to the study [2], we did not find a higher frequency of fractures in patients with hypertension. We did not study the relationship between fractures and liver and lung diseases. A well-known factor in increasing the frequency of comorbid conditions in patients undergoing hemodialysis, including fractures, is the presence of diabetes [2, 3, 13]. However, we did not establish this. The DOPPS II study (performed in 12 countries) also did not identify diabetes as an independent risk factor for femoral fractures or any other in hemodialysis patients [10]. Other factors, including anemia, intradialysis hypotension, and diabetic polyneuropathy, may be associated with dizziness and falls, increasing the incidence of fractures in hemodialysis patients [6, 11, 12].

CKD is associated with hyperphosphatemia, hypocalcemia, increased PTH, reduced activation of vitamin D and its deficiency, uremia. This leads to abnormal changes in the microarchitectonics of compact and cancellous bone [12]. The coccyx plays a key role in providing mechanical strength, so any changes in its structure increase the risk of fracture. We demonstrated that a serum albumin level below 31.4 g/l is a risk factor for fracture, consistent with the DOPPS II study [10, 12]. In addition, they showed that the level of alkaline phosphatase over 197.7 units/l and the level of vitamin D 23.5 mmol/l and below were independent predictors of the development of fractures, which definitely requires correction of these indicators. The level of PTH, especially in combination with hyperphosphatemia, also contributed to the occurrence of fractures, as shown in some studies [2–4]; however, some experts [1] deny the relationship of PTH concentration in blood serum with the risk of fractures.

Our study had some limitations. First, we did not analyze data on the specific diagnosis of osteoporosis using dual-energy X-ray absorptiometry (DEXA), taking into account that DEXA assessment of bone mineral density in patients with end-stage renal disease has limitations [11].

In addition, the study included fractures in only a small portion of the country's dialysis population.

Conclusions

A significant, almost doubled, increase in the frequency of fractures ($p < 0.0001$) was found in patients with CKD VD stage who were administered hemodialysis during a three-year follow-up ((35.5 ± 17.8) months).

In the structure of fractures in patients with CKD VD stage who received hemodialysis, both at the beginning and at the end of the study, femoral fractures prevailed over other localizations. An increase in the specific weight of patients with fractures by 96 % was found during the prospective observation and the incidence rate was 5.8 per 100 p/y.

Independent predictors of the development of fractures in patients with CKD stage VD undergoing hemodialysis were established as follows: age over 49 years, serum alkaline phosphatase level over 197.7 units/l, vitamin D — 23.5 mmol/l and less, albumin — 31.4 g/l and less.

An increase in serum PTH concentration in combination with hyperphosphatemia was shown to result in fractures.

The developed method for assessing the risk of fractures for patients with CKD VD stage undergoing hemodialysis is individualized, accessible in execution and interpretation, allows physicians to identify individuals with an increased risk of developing fractures using standard basic clinical and laboratory indicators.

Conflict of interest. The authors declare no conflict of interest.

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PREDICTORS OF FRACTURES IN PATIENTS WITH STAGE VD CHRONIC KIDNEY DISEASE TREATED WITH HEMODIALYSIS

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